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Bilevel ventilation during exercise in acute on chronic respiratory failure: A preliminary study

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Summary
To determine the immediate effects of bilevel non-invasive ventilation plus oxygen (NIV + O_2) during exercise compared to exercise with O_2 alone in people recovering from acute on chronic hypercapnic respiratory failure (HRF), a randomised crossover study with repeated measures was performed.

Eighteen participants performed six minute walk tests (6MWT) and 16 participants performed unsupported arm exercise (UAE) tests with NIV + O_2 and with O_2 alone in random order.

Distance walked increased by a mean of 43.4 m (95% CI 14.1 to 72.8, $p = 0.006$) with NIV + O_2 compared to exercise with O_2 alone. In addition, isotime oxygen saturation increased by a mean of 5% (95% CI 2–7, $p = 0.001$) and isotime dyspnoea was reduced [median 2 (interquartile range (IQR) 1–4) versus 4 (3–5), $p = 0.028$] with NIV + O_2. A statistically significant increase was also observed in UAE endurance time with NIV + O_2 [median 201 s (IQR 93–414) versus 157 (90–342), $p = 0.033$], and isotime perceived exertion (arm muscle fatigue) was reduced by a mean of 1.0 on the Borg scale (95% CI −1.9 to −0.1, $p = 0.037$) compared with O_2 alone.

Non-invasive ventilation plus O_2 during walking resulted in an immediate improvement in distance walked and oxygen saturation, and a reduction in dyspnoea compared to exercise with O_2 alone in people recovering from acute on chronic HRF. The reduction of dyspnoea during walking and arm muscle fatigue during UAE observed with NIV + O_2 may allow patients to better tolerate exercise early in the recovery period.

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Introduction

Patients with chronic hypercapnic respiratory failure (HRF) have a decreased exercise capacity and reduced activity levels compared to healthy controls.[1,2] They often report severe exertional dyspnoea[3] and have limited ventilatory reserve during exercise.[4,5] With the development of acute on chronic HRF, ventilatory capacity decreases further.[6,7] Consequently, severe dyspnoea[8] and unstable gas exchange may delay the onset of exercise rehabilitation and place patients at risk of further deconditioning.

Non-invasive ventilation during exercise has been shown to reduce dyspnoea in proportion to respiratory muscle unloading,[9,10] improve gas exchange,[11–13] and increase endurance time compared to unassisted exercise in patients with chronic HRF secondary to severe COPD[3,11] and severe restrictive chest wall disorders.[14–16] While invasive mechanical ventilation during walking has been described in stable hospitalised ventilator-dependent patients[8,17,18] and during supported arm exercise (SAE) in difficult to wean patients with COPD and HRF,[19] the effect of non-invasive ventilation plus oxygen (NIV + O_2) during walking or during functional (unsupported) arm exercise compared to standard therapy (exercise with O_2 alone) is unknown in patients recovering from acute on chronic HRF. If NIV + O_2 during exercise can provide similar benefits to patients recovering from acute HRF as in stable patients with HRF, it may permit exercise rehabilitation to be commenced earlier in the hospital stay, thus reducing the risk of further deconditioning.

The aim of the present study was to determine the effects of bilevel NIV + O_2 during ground walking and unsupported arm exercise (UAE) on exercise capacity compared to exercise with O_2 alone in people recovering from acute on chronic HRF. We hypothesised that NIV + O_2 during exercise would reduce dyspnoea, improve oxygenation and allow patients to exercise for longer compared with O_2 alone.

Method

Participants

Fourteen participants recovering from acute on chronic HRF performed a series of six minute walk tests (6MWT) and a series of UAE tests. An additional four participants performed the 6MWT only, giving a total of 18 participants who performed the series of 6MWT. An additional two participants performed UAE tests only, giving a total of 16 participants who performed the series of UAE tests. Participant characteristics are described in Table 1. Inclusion criteria were all of the following: admitted to hospital with acute on chronic HRF (pH $<$ 7.35, $PaCO_2$ $>$ 45 mmHg, HCO_3^- $>$ 26 mmol/L) that required ongoing treatment with NIV; history of severe chronic lung disease or severe chest wall restrictive disorder; dyspnoea as the primary symptom that limited daily activities. Bilevel NIV was commenced if the respiratory acidosis (pH $<$ 7.35) persisted despite judicious use of supplemental O_2 therapy. Standard medical therapy was instituted in conjunction with NIV and included, but was not limited to, supplemental O_2, bronchodilators, antibiotics, corticosteroids and diuretics where indicated. Exclusion criteria at the time of exercise testing were any of the following: unable to tolerate $>$1 h off NIV; arterial pH $<$ 7.35; temperature $>$38 °C; SpO_2 $<$ 88% at rest with a fraction of inspired oxygen $\geq$0.5; resting systolic blood pressure $<$90 mmHg or $>$160 mmHg; resting diastolic blood pressure $<$60 mmHg or $>$100 mmHg; unstable angina or a myocardial infarct during the previous month; resting heart rate (HR) $>$120 beats/min; or decreased level of consciousness.

Study design and protocol

A randomised crossover study with repeated measures was performed on an ambulatory respiratory medicine ward of a large teaching hospital with a dedicated acute NIV service.

Participants were asked to perform two six minute walk tests (6MWT) and two UAE tests. In those participants who performed both 6MWT and UAE tests, the order of testing was randomised. In addition, the order of 6MWT with O_2 alone and with NIV + O_2 was randomised, and the order of UAE with O_2 alone and with NIV + O_2 was randomised. If a participant was unable to perform both series of 6MWT and UAE tests due to a musculoskeletal or neurological condition that affected the upper or lower limbs, the type of test the participant was able to perform was selected. The randomisation scheme was generated using a web site (http://www.Randomization.com) and test order was concealed in a sealed, opaque envelope until written consent was obtained from participants. All tests were completed within one day. Ethical approval was obtained from the Human Ethics Committee of Sydney South West Area Health Service and The University of Sydney. The study was registered as part of a larger trial with the Australian New Zealand Clinical Trials Registry (ACTRN12605000215628).

One hour prior to the two 6MWTs, a practice 6MWT was conducted with NIV + O_2 to familiarise participants to the test[20] and to walking with NIV. Similarly, one hour prior to the two UAE tests, a practice UAE test was conducted with O_2 alone to familiarise participants to the test. Participants rested for at least one hour between each 6MWT and at least one hour between each UAE test and until SpO_2, HR, dyspnoea and perceived exertion scores returned to baseline. Oxygen flow was delivered to ensure a resting SpO_2 of approximately 93% and was not adjusted further during exercise. Standardised encouragement was given each minute during exercise. Participants were instructed to exercise until they felt too breathless or fatigued to continue. The investigator paused the 6MWT or stopped the UAE test if SpO_2 $<$ 75% during exercise. In addition, the UAE test was terminated if participants could not keep in time with the metronome.

Exercise tests

Six minute walk test

The 6MWT was performed according to the American Thoracic Society guidelines[21] with two exceptions. Firstly, participants used a forearm support frame to enable them to walk safely and independently, and secondly, a research assistant pushed a trolley containing the bilevel machine and related equipment behind the participant during each 6MWT.

Table 1 Participant characteristics.

	6MWT ($n = 18$)	UAE test ($n = 16$)
Age yrs	65 (61—68)	64 (56—66)
F/M	10/8	8/8
BMI kg m^{-2}	27.2 ± 8.3	27.6 ± 8.0
Diagnostic group (n)		
COPD	12	12
Bronchiectasis	2	2
Cystic fibrosis	1	1
Kypho/scoliosis	3	1
Domiciliary NIV (prior to admission)	4	5
Reason for acute on chronic HRF (n)		
AECOPD	12	11
Respiratory tract infection	6	6
Pulmonary oedema	1	1
Hyperoxia	6	5
ABG on admission		
pH	7.30 ± 0.05	7.30 ± 0.04
$PaCO_2$ mmHg	73.8 ± 15.3	71.6 ± 15.0
PaO_2 mmHg	68.5 (51.0—95.0)	76.5 (58.0—97.0)
HCO_3^- mmol/L	32.0 (29.0—39.0)	32.8 ± 5.3
SaO_2%	94.0 (89.0—97.0)	92.3 (90.0—97.0)
Supp O2 (L/min)	2.7 ± 2.1	2.0 (1.0—2.5)
NIV use 24 h prior to the study		
Number of participants on NIV	18	16
Hours	10.9 ± 5.1	11.0 ± 4.6
ABG prior to exercise tests		
pH	7.39 ± 0.03	7.39 ± 0.03
$PaCO_2$ mmHg	58.6 ± 9.1	57.9 ± 8.9
PaO_2 mmHg	70.3 ± 17.8	72.9 ± 17.5
HCO_3^- mmol/L	34.0 ± 5.8	33.9 ± 5.0
SaO_2%	92 ± 5	93 ± 4
Supp O_2 (L/min)	3.0 (2.0—4.0)	2.0 (1.0—2.0)
Pulmonary function		
FEV_1% predicted	21 (16—27)	21 (16—24)
FVC% predicted	45 ± 21	48 ± 22
FEV_1/FVC%	46 ± 17	43 ± 13
$PI_{max1.0}$ cmH_2O% predicted	54 ± 28	65 ± 27
NIV settings during exercise		
IPAP cmH_2O	15.5 (15.0—18.0)	15.8 ± 1.6
EPAP cmH_2O	5.0 (4.0—5.0)	5.0 (5.0—5.0)
PS (IPAP—EPAP) cmH_2O	11.0 (10.0—13.0)	10.5 (10.0—12.0)

Data are presented as mean ± SD or median (interquartile range). 6MWT: six minute walk test; UAE: unsupported arm exercise; F/M: female/male; BMI: body mass index; COPD: chronic obstructive pulmonary disease; NIV: non-invasive ventilation; AECOPD: acute exacerbation of chronic obstructive pulmonary disease; ABG: arterial blood gas; $PaCO_2$: arterial carbon dioxide tension; PaO_2: arterial oxygen tension; HCO_3^-: arterial bicarbonate ion concentration; SaO_2: oxygen saturation; Supp O2: supplemental oxygen; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; $PI_{max}1.0$: plateau maximal inspiratory mouth pressure; IPAP: inspiratory positive airway pressure; EPAP: expiratory positive airway pressure; PS: pressure support. Note: participants occasionally had more than one reason for admission to hospital.

Unsupported arm exercise test

An externally paced unsupported arm exercise test as described by Takahashi and colleagues[22] was modified to measure endurance rather than peak exercise capacity. The test required the seated participant to lift a weighted dowel from waist height to increasingly higher levels on a chart. The pace of lifting was one lift every two seconds in time with a metronome. In a practice test, after five repetitions (10 s) at each level, participants progressed through the levels on the chart until they reached a level that they deemed to be a moderate workload on the rate of perceived exertion (RPE) scale (score of 3). Participants were instructed to exercise at this level for as long as possible. The same level on the chart that was achieved in the practice test was used for the two subsequent UAE tests.

Measures

Anthropometric data, an arterial blood gas, spirometry (Microloop™, Micromedical Limited, Rochester, Kent, England) and maximum inspiratory occlusion mouth pressures (Morgan Medical Limited, Gilingham, England) were collected prior to testing. Participants then sat quietly for ten minutes breathing supplemental O_2 prior to O_2 tests or breathing with NIV + O_2 prior to NIV + O_2 tests before baseline measures of SpO_2, HR, dyspnoea and RPE (leg muscle exertion for 6MWTs and arm muscle exertion for UAE tests) were recorded. Oxygen saturation and HR were recorded continuously during exercise using a pulse oximeter (Radical™, Massimo, Irvine CA, USA). Dyspnoea and RPE[23] were measured on a 0–10 category-ratio scale at baseline, every 30 s during exercise, and at end exercise. Blood pressure was measured manually at baseline and end exercise.

Non-invasive ventilation

Non-invasive ventilation was delivered using a pressure preset bilevel machine (VPAPIII ST™, ResMed, Sydney, Australia) via a full face mask (Ultra-mirage™, ResMed, Sydney, Australia; or, Comfort-Full™, Respironics, Murrysville, PA, USA). The bilevel machine was set in the spontaneous mode with an expiratory positive airway pressure (EPAP) of 4–5 cmH_2O. Inspiratory positive airway pressure (IPAP) was set 10 cmH_2O above EPAP and was increased at rest to a level of comfort. Exercise settings are described in Table 1. The inspiratory trigger threshold was 4.5 L/min and maximum inspiratory flow rate was 170 L/min. The minimum rise time (time from EPAP to IPAP) of 100 ms was used. Supplemental O_2 was added via a t-piece near the air outlet of the machine. A 12-volt external battery powered the bilevel machine during walking.

Data analysis and statistics

The primary outcome measure for the 6MWT was total distance walked. Secondary outcome measures were distance and time to first rest, isotime SpO_2 and dyspnoea. Isotime was defined as the earliest time-point where the participant rested during either 6MWT. Dyspnoea scores and SpO_2 from NIV + O_2 and O_2 tests were compared at this point in time. To detect a 48 metre change in 6MWD[24] with NIV + O_2, using a SD estimate of 51 m (based on data from the first 5 participants), power of 0.8, and α of 0.05, a sample of 18 participants was required. For UAE, the primary outcome measure was endurance time and secondary outcome measures were isotime SpO_2 and dyspnoea, where isotime was defined as the end point of the shorter endurance test. To detect a 30 s change in UAE endurance time with NIV + O_2, using a SD estimate of 39 s (based on data from the first 5 participants), power of 0.8, and α of 0.05, a sample of 16 participants was needed.

Descriptive data for continuous variables with a normal distribution are presented as mean ± standard deviation (SD), or median and interquartile range (IQR) for data that failed the Kolmogorob-Smirnov normality test. Paired t-tests, or Wilcoxon signed rank tests for non-parametric data, were conducted to determine if there was a difference between exercise with NIV + O_2 and exercise with O_2 alone with respect to the primary and secondary outcome measures. A significance level of $p < 0.05$ was used for all comparisons.

Results

The median time from hospital admission to performance of the exercise tests was 4 days (IQR 2–7). All participants completed the exercise tests. Oxygen saturation fell below 75% in three participants during the 6MWT with O_2. No adverse events occurred.

Six minute walk test

Exercise with NIV + O_2 significantly increased total distance walked by a mean 43.4 m (95% CI 14.1–72.8, $p = 0.006$) compared to exercise with O_2 alone (Table 2, Fig. 1a). In addition, distance to first rest, time to first rest and isotime SpO_2 were increased, while isotime dyspnoea was decreased with NIV + O_2 during walking (Table 2, Fig. 1b). The primary symptom limiting walking was dyspnoea (NIV + O_2: $n = 14$; O_2 alone: $n = 17$), leg muscle fatigue (NIV + O_2: $n = 2$; O_2 alone: $n = 0$), or a combination of dyspnoea and leg muscle fatigue (NIV + O_2: $n = 2$; O_2 alone: $n = 1$). There was no effect of test order on any of the primary or secondary outcome measures.

Unsupported arm exercise

There was a statistically significant increase in UAE endurance time with NIV + O_2 compared to exercise with O_2 alone [median 201 s (IQR 93–414) versus 157 s (90–342), $p = 0.033$] (Table 3, Fig. 2a). There was no difference in isotime SpO_2 or dyspnoea with NIV + O_2. However, isotime RPE was reduced compared to exercise with O_2 alone (Table 3, Fig. 2b). The primary symptom limiting UAE was arm muscle fatigue (NIV + O_2: $n = 15$; O_2 alone: $n = 14$), dyspnoea (NIV + O_2: $n = 1$; O_2 alone: $n = 1$), or a combination of arm muscle fatigue and dyspnoea (O_2 alone: $n = 1$). There was no effect of test order on any of the primary or secondary outcome measures.

Discussion

The main findings of the present study were that bilevel NIV + O_2 during ground walking increased distance walked, improved SpO_2 and reduced dyspnoea compared to exercise with O_2 alone in patients recovering from acute on chronic HRF. An improvement in UAE endurance time was also found with NIV + O_2 compared to exercise with O_2 alone, and was associated with a reduction in arm muscle fatigue. Exercise performed several days after admission to hospital was safe and well tolerated in these patients.

Improvements in exercise capacity and dyspnoea have been observed after exercise training in patients recovering from acute respiratory failure.[8,25] However, severe dyspnoea[8] and unstable gas exchange can delay activity and place patients at risk of further deconditioning in the early

Table 2 Six minute walk test with oxygen (O_2) alone compared with non-invasive ventilation plus oxygen (NIV+O_2).

	O_2	NIV + O_2	Mean difference (95% CI)	*p*
Rest				
SpO_2 (%)	93 (92–96)	95 (93–98)	FN	<0.000
Supp O_2 (L/min)	1.5 (0.5–3.0)	1.5 (0.5–3.0)	FN	0.75
HR (beats/min)	90 ± 14	91 ± 17	1 (−3 to 4)	0.61
Dyspnoea (Borg)	0.5 (0–0.8)	0.3 (0–0.8)	FN	0.32
RPE (Borg)	0 (0–0.5)	0 (0–0.5)	FN	0.28
SBP (mmHg)	125.0 ± 17.7	123.6 ± 14.1	−1.4 (−8.6 to 5.7)	0.68
DBP (mmHg)	73.0 ± 13.0	77.5 ± 7.0	4.5 (−1.7 to 10.7)	0.14
MAP (mmHg)	90.3 ± 12.0	92.8 ± 8.9	2.5 (−2.7 to 7.6)	0.32
Isotime				
SpO_2 (%)	87 ± 6	92 ± 5	5 (2 to 7)	0.001
HR (beats/min)	109 ± 14	108 ± 15	−2 (−4 to 1)	0.15
Dyspnoea (Borg)	4.0 (3.0–5.0)	2.0 (1.0–4.0)	FN	0.028
RPE (Borg)	3.0 (2.0–5.0)	3.0 (1.0–3.0)	FN	0.46
End exercise				
SpO_2 (%)	89 ± 7	90 ± 6	2 (−2 to 6)	0.26
HR (beats/min)	109 ± 14	108 ± 20	−1 (−8 to 6)	0.72
Dyspnoea (Borg)	4.9 ± 2.9	5.4 ± 3.0	0.4 (−0.6 to 1.5)	0.37
RPE (Borg)	4.4 ± 3.1	4.9 ± 3.0	0.8 (−0.8 to 1.8)	0.41
SBP (mmHg)	140.2 ± 17.4	140.1 ± 15.6	−0.7 (−5.5 to 4.1)	0.76
DBP (mmHg)	80.2 ± 11.9	83.5 ± 9.6	3.1 (−0.5 to 6.7)	0.086
MAP (mmHg)	100.2 ± 12.9	102.4 ± 11.0	1.8 (−1.4 to 5.0)	0.24
Total distance (m)	187.5 ± 89.9	230.9 ± 114.8	43.4 (14.1 to 72.8)	0.006
Distance to 1st rest (m)	159.8 ± 97.1	221.4 ± 119.8	61.6 (19.6 to 103.6)	0.007
Time to 1st rest (s)	188 (151–360)	360 (284–360)	FN	0.012

Data are presented as mean ± SD or median (interquartile range). O_2: oxygen; NIV + O_2: non-invasive ventilation plus oxygen; SpO_2: oxygen saturation; Supp O_2: supplemental oxygen; HR: heart rate; RPE: rate of perceived exertion; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; FN: failed normality test.

stages of recovery. The detrimental effects of prolonged bed rest on muscle strength and function are well described.[26] Currently, there are no evidence-based recommendations regarding strategies to alleviate dyspnoea and improve functional exercise performance in the early stages of recovery from acute on chronic HRF. The present study provides novel information in this area.

Effect of non-invasive ventilation plus oxygen during ground walking

The present study is the first to demonstrate the benefits of NIV during walking in patients recovering from acute on chronic HRF. Total distance walked increased by a mean of 43.4 m, and distance to first rest increased by a mean of 61.6 m with NIV + O_2 compared to walking with O_2 alone. The minimal clinically important difference in 6MWD is not known in patients recovering from acute on chronic HRF. However, the change in 6MWD with NIV + O_2 is comparable to the mean change in 6MWD of 48 m (95% CI 32–65) after at least four weeks of supervised outpatient pulmonary rehabilitation in patients with COPD.[24] Median time to ''first rest'' was 6 min with NIV + O_2 compared to 3.1 min with O_2 alone, indicating that many participants completed the 6MWT with NIV + O_2 without stopping to rest. While it is unknown whether the changes observed are clinically significant, the reduction in dyspnoea and improvement in oxygenation observed suggest that NIV + O_2 during walking may allow patients to commence exercise earlier in the recovery phase, thus reducing the risk of deconditioning.

The mechanisms of improved walking performance with NIV + O_2 most likely relate to the reduction in dyspnoea and improvement in SpO_2 compared to walking with O_2 alone that was observed at isotime exercise. As dyspnoea was the primary symptom that limited walking in our participants, reduction of this unpleasant symptom with NIV + O_2 probably played a key role in allowing participants to walk further with fewer rests. In stable patients with COPD, NIV during exercise was found to reduce dyspnoea in proportion to respiratory muscle unloading.[9,10] Similarly in patients recovering from acute on chronic HRF, NIV may have unloaded the respiratory muscles, thereby reducing dyspnoea.

Oxygen saturation was higher with NIV + O_2 during exercise and this may have resulted in improved muscle oxygenation and contributed to the improvement in exercise performance.[27] In addition, patients with chronic HRF due to severe COPD or kyphoscoliosis can develop a combined respiratory and metabolic acidosis during exercise.[12,13] Acute hypercapnia with a respiratory acidosis can significantly impair respiratory muscle function.[28,29] In stable patients, NIV during exercise has been shown to reduce exercise induced hypercapnia and improve exercise performance.[12,13] However, the advantage of NIV + O_2 during walking over O_2 alone in preventing CO_2 retention in patients recovering from acute on chronic HRF is yet to be confirmed.

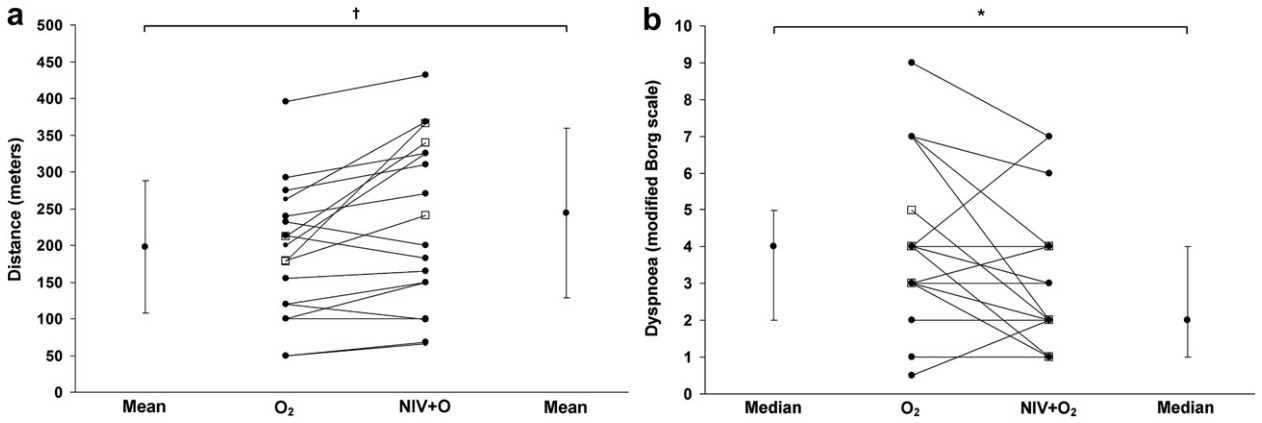

Figure 1 (a) Total distance walked during the six minute walk test with oxygen alone (O_2) compared with non-invasive ventilation plus oxygen (NIV + O_2). Whiskers represent standard deviation; (b) Isotime dyspnoea during the six minute walk test with oxygen alone (O_2) compared with non-invasive ventilation plus oxygen (NIV + O_2). Whiskers represent interquartile range. Closed circles represent data from participants with chronic obstructive lung disease; open squares represent data from participants with restrictive chest wall disorders; $^*p < 0.05$; $^\dagger p < 0.01$.

Finally, EPAP may have assisted participants with severe airflow limitation and intrinsic positive end expiratory pressure (PEEP) during walking. Dynamic hyperinflation commonly occurs during ground walking in patients with severe COPD and is associated with an increase in dyspnoea in proportion to the reduction in inspiratory capacity.[30] Application of external PEEP at rest has been shown to unload the respiratory muscles in patients with COPD and acute HRF with intrinsic PEEP.[31] Whether the application of EPAP during exercise can delay the onset or extent of dynamic hyperinflation remains to be demonstrated in patients recovering from acute on chronic HRF as well as in those with stable COPD.

Effect of non-invasive ventilation plus oxygen during unsupported arm exercise

While a statistically significant improvement in UAE endurance time was found with NIV + O_2 compared to exercise with O_2 alone, examination of individual data (Fig. 2) revealed that only a few participants demonstrated a substantial increase in endurance time. This is in contrast to a previous study performed by our group in patients with

Table 3 Unsupported arm exercise with oxygen (O_2) alone compared with non-invasive ventilation plus oxygen (NIV+O_2).

	O_2	NIV + O_2	Mean difference (95% CI)	*p*
Rest				
SpO_2 (%)	93 ± 2	94 ± 2	1 (0 to 2)	0.087
Supp O_2 (L/min)	2.0 (1.0—3.0)	1.0 (1.0—3.0)	FN	0.068
HR (beats/min)	91 ± 14	92 ± 16	1 (−2 to 4)	0.57
Dyspnoea (Borg)	0.8 (0—1.0)	0.8 (0—1.0)	FN	0.92
RPE (Borg)	0 (0—1.0)	0 (0—0.5)	FN	1.0
SBP (mmHg)	122.3 ± 15.2	120.8 ± 15.7	−1.5 (−5.9 to 2.9)	0.48
DBP (mmHg)	77.8 ± 10.7	77.8 ± 10.3	−0.1 (−2.9 to 2.8)	0.96
MAP (mmHg)	92.7 ± 11.6	92.1 ± 11.5	−0.6 (−3.3 to 2.2)	0.68
Isotime				
SpO_2 (%)	92 ± 3	93 ± 3	1 (1 to 3)	0.21
HR (beats/min)	100 ± 14	98 ± 19	−2 (−6 to 2)	0.26
Dyspnoea (Borg)	4.9 ± 3.1	4.0 ± 2.7	−1.0 (−2.2 to 0.3)	0.11
RPE (Borg)	6.6 ± 3.0	5.6 ± 3.1	−1.0 (−1.9 to −0.1)	0.037
End exercise				
SpO_2 (%)	92 ± 2	93 ± 3	1 (−1 to 3)	0.20
HR (beats/min)	101 ± 16	102 ± 16	1 (−1 to 3)	0.29
Dyspnoea (Borg)	5.1 ± 3.0	5.0 ± 2.8	−0.2 (−1.6 to 1.3)	0.82
RPE (Borg)	6.9 ± 2.8	6.7 ± 2.9	−0.3 (−1.1 to 0.6)	0.53
SBP (mmHg)	139.4 ± 18.6	134.7 ± 18.5	−4.7 (−9.5 to 0.1)	0.054
DBP (mmHg)	84.5 ± 10.9	81.8 ± 9.8	−2.7 (−5.7 to 0.3)	0.074
MAP (mmHg)	102.8 ± 12.3	99.4 ± 11.9	−3.3 (−6.3 to −0.4)	0.031
Endurance time (s)	157 (90—342)	201 (93—414)	FN	0.033

Data are presented as mean ± SD or median (interquartile range). Refer to Table 2 for abbreviations.

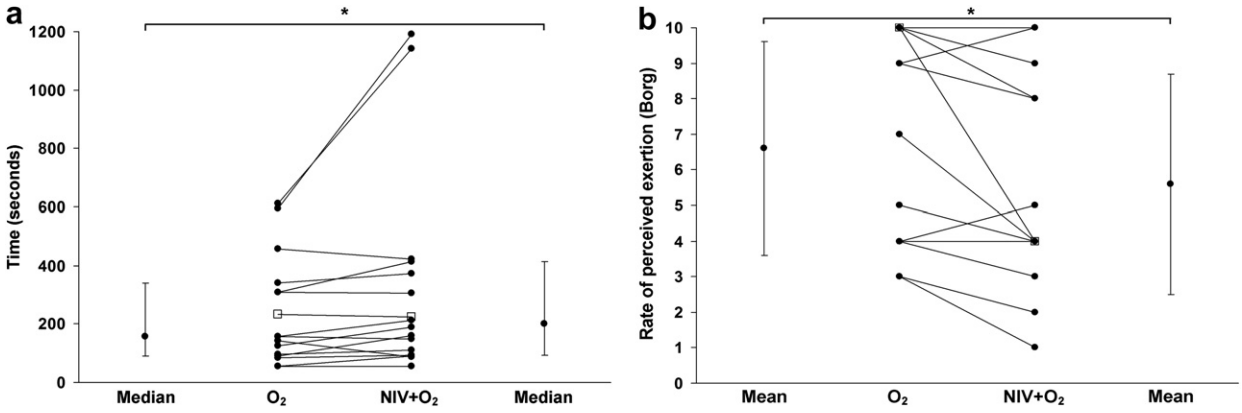

Figure 2 (a) Unsupported arm exercise endurance time with oxygen alone (O_2) compared with non-invasive ventilation plus oxygen ($NIV + O_2$). Whiskers represent interquartile range; (b) Isotime rate of perceived exertion during the unsupported arm exercise test with oxygen alone (O_2) compared with non-invasive ventilation plus oxygen ($NIV + O_2$). Closed circles represent data from participants with chronic obstructive lung disease; open squares represent data from participants with restrictive chest wall disorders; $*p < 0.05$.

stable chronic HFR, where NIV increased UAE endurance time by a mean of 91 s compared to exercise without NIV.[16] Pressure support during exercise has previously been shown to improve SAE capacity in people recovering from acute on chronic HRF who were slow to wean from mechanical ventilation.[19] Due to specificity of training, UAE is preferable over SAE for functional exercise training.[32] However, UAE is more difficult to perform than SAE because during UAE, some accessory respiratory muscles have a dual task of performing the upper limb activity as well as assisting respiration. Consequently, some of the ventilatory load is shifted to the diaphragm and abdominal muscles.[33]

In our participants, despite arm muscle fatigue being the primary symptom that limited UAE, severe dyspnoea (mean 4.9) was reported at isotime during exercise with O_2 alone. Non-invasive ventilation has previously been shown to unload the diaphragm during arm elevation in patients with chronic HRF.[34] The inverse relationship between respiratory muscle unloading and dyspnoea[9] has been discussed previously. We found a small non-significant reduction in isotime dyspnoea (mean 1.0) with $NIV + O_2$ compared to UAE with O_2 alone. This was considerably lower than the mean reduction in isotime dyspnoea of 2.3 that was found with NIV during UAE in stable patients with chronic HRF.[16] It is possible that the level of pressure support (IPAP−EPAP) delivered in the current study was too low to sufficiently unload the respiratory muscles during UAE in the majority of participants, and therefore to significantly reduce dyspnoea and cause a substantial increase in exercise endurance time.

In the present study, isotime RPE (arm muscle fatigue) was reduced by a mean of 1.0 on the Borg scale with $NIV + O_2$ during UAE which was similar to the reduction in isotime RPE observed in stable patients with chronic HRF.[16] Despite this reduction, the majority of participants eventually terminated UAE due to arm muscle fatigue whether $NIV + O_2$ or O_2 alone was used. The fatigue was most likely attributable to the effect of repetitive exercise in a small muscle group. However, even a small reduction of arm muscle fatigue may enable patients recovering from acute on chronic HRF to better tolerate UAE early in the recovery period.

The use of $NIV + O_2$ during exercise as part of routine clinical practice does have resource implications. Therefore, investigation of the cost-benefit relationship of such a strategy during early exercise rehabilitation in people recovering from acute on chronic HRF is warranted and should evaluate outcome measures including staff time, length of stay, functional exercise capacity, physical activity and quality of life following discharge.

Limitations

Neither participants nor investigators were blinded to NIV in this study. To minimise potential bias, standardised instructions and encouragement were given. Sham NIV was not used because an effective sham has not been identified for this population. In addition, we had to limit the number of tests performed to prevent excessive fatigue, and wanted to compare the effect of $NIV + O_2$ during exercise to usual clinical practice (exercise with O_2 alone) rather than sham.

Another potential limitation was that a heterogeneous group of patients were studied. While the mechanisms that contribute to dyspnoea and exercise limitation differ between patients with severe chronic lung disease and those with severe chest wall restriction, both groups often have very limited ventilatory reserve during exercise,[4,5] both have been shown to derive benefit from NIV during exercise when stable,[3,11,14,16] and examination of individual data (Figs. 1 and 2) does not suggest a particular pattern of response to NIV during exercise based on diagnostic group alone. In addition, disease severity appears to be an important factor that affects the response to NIV during exercise, even within patients from the same diagnostic group. This has been demonstrated in people with stable COPD,[3,35] kyphoscoliosis[14] and with CPAP during exercise in people with cystic fibrosis,[36] where those subjects with more severe disease achieved greater improvements with NIV or CPAP during exercise than those with less severe disease. The participants included in the

present study all had severe disease with a greatly reduced ventilatory capacity, and therefore presented as a group who may benefit from NIV + O_2 during exercise.

Conclusion

Bilevel NIV + O_2 during ground walking resulted in an immediate improvement in distance walked and SpO_2 compared to exercise with O_2 alone in people recovering from acute on chronic HRF. The combination of NIV + O_2 reduced dyspnoea during walking and arm muscle fatigue during UAE compared to exercise with O_2 alone and therefore may assist patients to tolerate exercise rehabilitation early in the recovery phase in an attempt to avoid deconditioning.

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Conflict of interest statement

The sleep laboratory of CM, AJP and DF previously received an industry-sponsored project grant from ResMed, Australia, and PAP equipment for other research projects from Air Liquide Australia and MayoHealthcare, Australia. AJP has received travel reimbursement from Weinmann, Germany and has also been paid for speaking and organising educational activities on behalf of the following bilevel machine manufacturers: ResMed, Australia; Respironics, Australia; Weinmann, Germany and Air Liquide, Australia. She has previously acted as a clinical consultant to ResMed. ERE and JAA have no conflict of interest regarding the present study.

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